The mixture was cooled and poured into cold water. The precipitated acid was extracted with ether and from the ether solution into dilute potassium hydroxide solution. This alkaline solution was acidified to precipitate the acid uncontaminated by amide. The acid was taken up in ether and the solution was dried and evaporated. Washing the residue with *n*-pentane (to remove a yellow coloration) gave white platelets.

Ethyl 3′-5,5-Dimethylbicyclo[2.2.1]heptan-1-ylpropionate.—A solution of 3′-5,5-dimethylbicyclo[2.2.1]heptan-1-ylpropionitrile (33 g.) in absolute ethanol (30 ml.) and dry ether (150 ml.) was saturated with hydrogen chloride, while being kept cooled in a freezing mixture. After storage overnight at −10°, the reaction mixture was concentrated by evaporation under reduced pressure. The solid imino-ester that separated was removed by filtration and then shaken up with water (750 ml.). The liberated ester was extracted with ether and purified by distillation.

3′-5,5-Dimethylbicyclo[2.2.1]heptan-1-ylpropanol.—Lithium aluminum hydride (2 g., 50% excess) was added to tetrahydrofuran (100 ml.) and refluxed with stirring for 30 min. After cooling the reaction vessel to room temperature, ethyl 3′-5,5-dimethylbicyclo[2.2.1]heptan-1-ylpropionate (31.4 g., 1.4 moles) was added dropwise with stirring. At the end of 12 hr., the excess of lithium aluminum hydride was decomposed by slow addition of water; sulfuric acid (4 *N*) was added to dissolve the aluminum hydroxide. Extraction with ether, followed by distillation, gave the desired alcohol.

2-Mesitylethanol.—In this preparation, the procedure described for the synthesis of mesitoic acid[24] from mesityl bromide was followed with the necessary modifications.

Into a 3-l. three-necked round-bottomed flask fitted with a condenser, stirrer, and dropping funnel was placed 16.8 g. (0.7 g.-atom) of magnesium turnings and 500 ml. of dry ether. A solution of ethyl bromide (38.5 g., 0.35 mole) and mesityl bromide (69.7 g., 0.35 mole) in ether (100 ml.) was added gradually over a period of 30 min. The reaction started as soon as the first portion of the bromide mixture was added. The reaction was completed by refluxing for another 30 min.

The reaction vessel was cooled in a bath of freezing mixture, and a solution of ethylene oxide (61.6 g., 70 ml., 1.4 moles) in ice-cold ether (100 ml.) was run in over 20 min. Within an hour, the reaction mixture turned into a gel. It was kept stirred overnight at room temperature. The Grignard complex was decomposed with 4 *N* sulfuric acid (500 ml.), the ether layer was removed, and the aqueous portion was extracted with ether. The combined ether extracts were dried and evaporated. The white solid residue was dried under vacuum and sublimed; white shiny crystalline scales were obtained.

2′-5,5-Dimethylbicyclo[2.2.1]heptan-1-ylethyl Bromide.—A solution of 2′-5,5-dimethylbicyclo[2.2.1]heptan-1-ylethyl tosylate (22.4 g., 0.07 mole) and lithium bromide (12 g., 100% excess) in dry acetone[9] (100 ml.) was refluxed with stirring for 24 hr. Most of the solvent was evaporated off and the residue was poured into water and extracted with ether.

Reaction of 2′-5,5-Dimethylbicyclo[2.2.1]heptan-1-ylethyl Tosylate with Potassium *t*-Butoxide.—The above tosylate (50 g.) was refluxed with 1 *N* solution (250 ml.) of potassium *t*-butoxide in anhydrous *t*-butyl alcohol for 20 hr. with stirring under anhydrous conditions. Potassium *p*-toluenesulfonate separated as a white precipitate during the reaction. The heterogeneous reaction mixture was poured into cold water (4000 ml.) and extracted with pentane. The dried pentane extract was evaporated and the residual liquid product was dried under vacuum. Small aliquots of the undistilled material were taken to determine the fraction of the olfinic product present; the olefin present was estimated using Wij reagent.[25] Fractionation gave 2′-5,5-dimethylbicyclo[2.2.1]heptan-1-ylethyl *t*-butyl ether.

The procedure described here was used without any major modification to study the reaction of alkoxides with other tosylates and bromides used in this investigation. When methoxide in methanol was used, the reaction mixture was refluxed for only 12 hr.

The relative amounts of olefin and ether formed in this and other related reactions are given in Table II.

Kinetic Study of the Reaction of *n*-Octadecyl Bromide and Tosylate with Potassium *t*-Butoxide.—The reaction was carried out in a 100-ml. volumetric flask. About 0.06 mole of the bromide (or tosylate) was placed in the volumetric flask and weighed. Then 0.9 *N* potassium *t*-butoxide in anhydrous *t*-butyl alcohol, already equilibrated thermally in a thermostat at 40°, was added to the calibration mark. The dissolution of the bromide was facilitated by shaking. The flask was kept in the thermostat and at suitable intervals 5.0-ml. aliquots of the contents were pipetted out into a titration flask containing 50 ml. of water. The amount of unneutralized base, and thereby the amount of bromide reacted, was determined by titrating with 0.06 *N* hydrochloric acid, using phenolphthalein as indicator.

The amount of olefin formed was determined in the following manner: the titrant from above was extracted with *n*-pentane, the extract dried (Na_2SO_4), and pentane evaporated.[26] The residue was dissolved in carbon tetrachloride (50 ml.) and the amount of olefin present was determined using Wij reagent.

A plot of t (sec.)/log $(a - x)$ $(b - x)$ was a straight line; a and b were initial concentrations of the bromide (or tosylate) and *t*-butoxide, respectively, and x was the amount of the substrate that had reacted. The reaction constant was obtained from the slope of the linear plot. The results of this kinetic study are given in Table I.

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(24) D. M. Bowen in "Organic Syntheses," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 553.

(25) A. Polgar and J. L. Jungnickel in "Organic Analysis," Vol. 3, Interscience Publishers, Inc., New York, N. Y., 1956, p. 222.

(26) When carbon tetrachloride was used for this extraction, it was found that some *t*-butyl alcohol was also extracted, which led to anomalous values in the subsequent titration of olefin.

[Contribution from the Defensive Research Division, Directorate of Defensive Systems, U. S. Army Chemical Research and Development Laboratories, Edgewood Arsenal, Md.]

Reactions of Isopropyl Methylphosphonofluoridate with Substituted Phenols. I

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A study has been made of the reactivity of isopropyl methylphosphonofluoridate with various substituted phenols. The data indicate that: (a) The nucleophilic displacement capability of a phenolate increases with the basicity of the anion ($\log k_2 = 0.589\text{p}K_a - 4.172$). (b) Cationic sites in the phenol increase the reactivity of the phenolate and the increase is inversely related to the distance between cationic and anionic sites. (c) There are marked steric (bulk) effects due to *ortho* substituents which lower the reactivity of the phenol. (d) Substances in the *ortho* position which are capable of hydrogen bonding can markedly increase the rate constant. (e) The reactivity of phenols in which the *ortho* substituent contains a cationic site can be adequately explained on the basis that two effects, opposite in their manifestations on the reactivity, are operative, *viz.*, b and c. A mathematical relationship to predict the reactivity of phenols containing cation sites is offered, and an explanation for "abnormal" reactivities shown by cationic phenols and others is advanced.

Investigations into the reactions of the nerve gas, isopropyl methylphosphonofluoridate (GB), in dilute aqueous solution have led to the discovery of classes of compounds which have high reactivity in displacement reactions with this organophosphorus compound.[1] Especially worthy of mention are metal salts,[2] metal chelates,[3] the anions of hypochlorous acid,[4] hydroxamic acids,[5] isonitrosoketones,[6] the monoanions of catechols,[7] and hydrogen peroxide.[8]

Where sufficient investigation has been made, series of related reagents have given typical Brønsted relationships[5b–e,7c] in their reaction with GB with the reactivity increasing as the basic strength ($1/K_a$ of the conjugate acid) of the nucleophile increased. But it also has been observed that different nucleophiles of similar basicity have widely differing reactivities[5d] and it appears that basicity, a very important factor in nucleophilic displacement reactivity of phosphorus esters, is not the only one. Nor has it been possible to attribute the high reactivity to a polarizability factor; highly polarizable sulfur-containing anions are poor nucleophiles in phosphorus displacement reactions.[4] To explain the high reactivity of the catecholates, hydroxamates, metal salts and chelates, and the anions of hypochlorous acid and hydrogen peroxide, a simultaneous and concerted "push-pull" on the phosphorus and oxygen or fluorine of the phosphorus ester by the nucleophile has been postulated.[2a,3a,b,4,5b,c,7a,c,8] Convincing evidence that a bifunctional attack of this type can occur and result in a high rate of reaction has been presented by Swain and Brown[9]; and the structural requirements for a bifunctional attack on the phosphorus ester, *viz.*, nucleophilic and electrophilic groups in proper spatial arrangement, are met by the above named reagents. Nevertheless, subsequent studies have shown that a hydroxamic acid anion incapable of assuming a structure which would possess bifunctional capability still has a reactivity with GB comparable to that of other hydroxamic acid anions of like basic strength.[5d] Moreover, it has been found in displacement reactions on *p*-nitrophenyl acetate that the methyl peroxide anion (which is incapable of bifunctional attack) is just as effective a nucleophile as is the hydroperoxide anion, and it was concluded that the reactivity of the anions of hydrogen peroxide and methyl hydroperoxide is not due to a concerted attack, but may be correlated with the high polarizabilities of the anions.[10] A more recent postulation is that the high nucleophilicity shown by certain molecules is due to "α" effect,[11] a requirement for which is that the nucleophile have an unshared pair of electrons in the position α to the site of high electron density.

Concerning the explanation for the high displacement reactivity shown by metal salts and chelates, there is again a difference of opinion. Some feel that a bifunctional attack is probable[2a,3a,b]; others prefer to write the reaction as occurring in two steps, an initial polarization of the GB molecule by the metal chelate followed by an attack upon the phosphorus by hydroxyl ion.[12]

While the explanation that the high reactivity of catechols with GB is due to a bifunctional concerted attack appears plausible, quantitative data on other substituted phenols to support (or contradict) this hypothesis were lacking. It was our original purpose to supply such data. To obtain additional evidence for support of the thesis that hydrogen bonding was, for the most part, responsible for the increased activity shown by the catechols, other phenols possessing *ortho* substituents capable of hydrogen bonding were sought for inclusion in our tests. Salicylamine and *o*-dimethylaminoethylphenol (the Mannich base of phenol) were selected inasmuch as they, in addition to having the hydrogen-bonding capabilities, also possessed phenol ionization constants of the same order as some of the catechols previously tested. These compounds showed the expected enhanced reactivities relative to their basic strengths, but the *m*- and *p*-substituted aminomethyl- and dimethylaminomethylphenols also showed higher than predicted reactivities. This observation led to the synthesis and evaluation of the reactivity of a number of aminoalkyl-, quaternary aminoalkylphenols, and several *o*-substituted phenols.

The data obtained and their interpretation form the gist of this report.

Experimental

(a) **Materials.**—In general, the phenols used herein were obtained from commercial sources and used without further purification if their melting points were sharp and in agreement with published literature values. In other cases, the compounds were recrystallized to constant melting point. 3-Hydroxyphenyltrimethylammonium iodide (m.p. 177°) was prepared by reaction of methyl iodide with *m*-dimethylaminophenol in ether at room temperature. 2-Hydroxyphenyltrimethylammonium iodide (m.p. 209°) and 4-hydroxyphenyltrimethylammonium iodide (m.p. 199–200°)[13] were prepared from the corresponding aminophenols by reaction with methyl iodide in the presence of sodium carbonate.[14] *m*-Hydroxybenzylamine hydrochloride (m.p. 147–148°) was prepared by heating *m*-methoxybenzylamine hydrochloride[15] with 12 N HCl in a Carius tube at 160° for 2 hr. and recrystallization from ethanol–ether solution. *p*-Hydroxybenzylamine hydriodide (m.p. 188°)[16] was prepared by heating *p*-methoxybenzylamine with constant boiling hydriodic acid in a sealed tube at 150° for 1 hr. and recrystallization from ethanol–ether solution. *m*-Hydroxybenzyldimethylamine hydrochloride (m.p. 172°) and *p*-hydroxybenzyldimethylamine hydrochloride (m.p. 184°) were prepared from the corresponding methoxy compounds by heating in a sealed tube with concentrated hydrochloric acid at 160° for several hours. 2-Hydroxybenzyltri-

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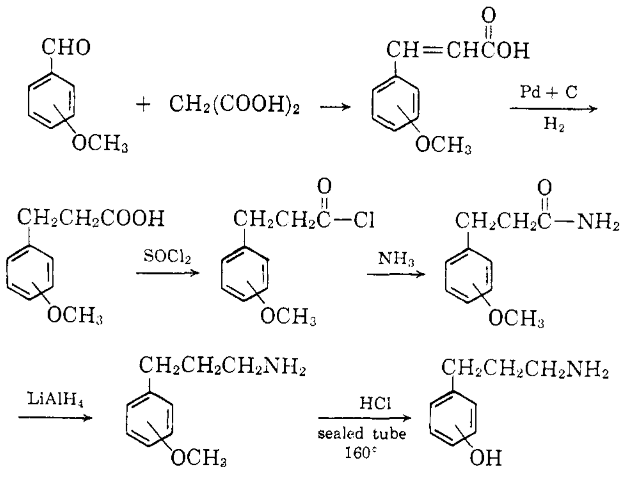
methylammonium iodide (m.p. 160°) and the corresponding 3-hydroxy compound (m.p. 177°) were prepared by stirring the respective tertiary amines with excess methyl iodide in dry ether for 8 hr. at room temperature and recrystallizing from ethanol–ether solution. To prepare the 4-hydroxy compound, 4-methoxybenzyltrimethylammonium iodide (m.p. 156°) was first prepared from methoxybenzyldimethylamine and excess methyl iodide as described above. Cleavage of the 4-methoxy compound by heating with constant boiling hydriodic acid at 140° for 5 hr. resulted in the desired 4-hydroxytrimethylammonium iodide (m.p. 185°). To prepare the hydroxyphenethylamines, the methoxybenzaldehydes were treated with nitromethane using ammonium acetate as condensing agent according to well established procedures.[17] The methoxy-β-nitrostyrenes so produced were reduced to the corresponding methoxyphenethylamines by a slight modification of standard lithium aluminum hydride reduction procedures.[18] To the cold hydride (0.25 mole) in 150 ml. of ether or tetrahydrofuran was added 0.084 mole of the nitroolefin. The mixture was refluxed for 6 hr., cooled, and the unused hydride destroyed by successively adding 3 ml. of water, 4 ml. of 20% NaOH solution, and 14 ml. of water.[19] The 2-methoxy compound (b.p. 74° (0.2 mm.), $n^{26.5}\mathrm{D}$ 1.5382; HCl salt m.p. 146°) and the 3-methoxy compound (b.p. 79° (1 mm.), $n^{27.5}\mathrm{D}$ 1.5362; HCl salt m.p. 130°) were converted to the corresponding hydroxy compounds by heating with 12 *N* HCl at 160° for several hours in a sealed tube. 2-Hydroxy-β-phenethylamine hydrochloride melted at 155°; 3-hydroxy-β-phenethylamine hydrochloride, at 134–136°. 2- and 4-hydroxyphenethyldimethylamines (m.p. as the hydrochlorides 115° and 183°, respectively) were prepared by heating in a sealed tube with 12 *N* HCl at 160° for several hours the 2- (b.p. 68° (0.4 mm.), $n^{28}\mathrm{D}$ 1.5101) and 4- (b.p. 92–95° (1.5 mm.), 101° (2.5 mm.), $n^{25}\mathrm{D}$ 1.5350; m.p. HCl salt 170°) methoxyphenethyldimethylamines. The methoxy compounds were prepared by reduction of the corresponding methoxyphenylacetonitriles with $LiAlH_4$[19] followed by reductive alkylation with formaldehyde.[20] The following sequence of reactions was used to prepare 3-hydroxy-β-phenethyldimethylamine hydrochloride: 3-methoxyphenylacetic acid was converted to the acyl chloride (b.p. 102° (25 mm.), $n^{25.5}\mathrm{D}$ 1.5375) with thionyl chloride. The acyl chloride was converted to 3-methoxyphenyl-N,N-dimethylacetamide (b.p. 123° (0.28 mm.), $n^{29.5}\mathrm{D}$ 1.5344) by reaction with dimethylamine in dry benzene. Lithium aluminum hydride reduction of the acetamide as previously described (see ref. 19) gave the methoxyphenethyldimethylamine (b.p. 81° (0.3 mm.), $n^{25.5}\mathrm{D}$ 1.5125; m.p. of HCl salt 133°). The hydroxy compound was obtained, as in previous cases, by heating with 12 *N* HCl in a sealed tube for several hours at 160°; m.p. for the HCl salt 163°. The 2-, 3-, and 4-hydroxy-β-phenethyltrimethylammonium iodides (m.p. 228–230°, 142°, and 235°) were prepared by treating the corresponding tertiary amines with methyl iodide in dry ether at room temperature as previously described. Ethanol–ether solvent was used for recrystallization.

The hydroxy-γ-phenylpropylamines were synthesized according to the following reactions.

The procedure of Walling and Wolfstirn[21] was followed for synthesis of the cinnamic acids from the benzaldehydes. Reduction to the phenylpropionic acids was accomplished by catalytic hydrogenation[21]; $LiAlH_4$ reductions of the amides of those acids were carried out in accordance with well established procedures.[22] The physical constants of the intermediates and desired products agreed well with published values.

The hydroxy-γ-phenylpropyldimethylamines were synthesized according to the reaction sequence shown below except that dimethylamine was used in place of ammonia. The m.p.'s of the 2-, 3-, and 4-hydroxy compounds as the hydrochloride salts are 155–157°, 91–93°, 145–146°, respectively.



The hydroxy-γ-phenylpropyltrimethylammonium iodides were synthesized from the corresponding hydroxy-γ-phenylpropyldimethylamine hydrochlorides. The free base was extracted from saturated sodium bicarbonate solution of the hydrochloride with ether. The ammonium salt was formed by allowing the free base to react with methyl iodide in ether at room temperature. The m.p.'s of the 2-, 3-, and 4-hydroxy-γ-phenylpropyltrimethylammonium iodides are 177°, 159–160°, 205–208°, respectively. Elemental analyses of all the compounds and intermediates synthesized were in good agreement with the calculated values.

To synthesize *o*-neopentylphenol, anisyl *t*-butyl ketone was first prepared by reaction of anisolelithium and pivaloyl chloride. The ketone was reduced[23] to *o*-neopentylanisole which was cleaved with hydrobromic acid to the desired phenol. The synthetic details follow.

Anisole *t*-Butyl Ketone.—Anisolelithium, prepared by mixing 0.4 mole of bromoanisole with 0.8 mole of lithium in 300 ml. of dry ethyl ether, was added with stirring to 200 ml. of a cold (ice bath), dry ether solution containing 0.4 mole of pivaloyl chloride over a 2-hr. period. After allowing the mixture to come to room temperature, 200 ml. of 2 *N* NaOH solution was added and the mixture was stirred vigorously for 1 hr. The ether layer was separated and dried over magnesium sulfate. The residue, after stripping of the solvent under reduced pressure, was fractionally distilled, the fraction boiling at 137° (12 mm.) containing the desired ketone; yield *ca.* 60%, $n^{27}\mathrm{D}$ 1.5020.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39; O, 16.64. Found: C, 74.4; H, 8.30; O, 17.10.

The 2,4-dinitrophenylhydrazone of anisyl *t*-butyl ketone melted at 140°.

Anal. Calcd. for $C_{18}H_{20}N_4O_5$: C, 58.06; H, 5.41. Found: C, 58.03; H, 5.22.

***o*-Neopentylanisole.**—Anisyl *t*-butyl ketone (0.14 mole) was stirred under reflux with hydrazine hydrate (1.4 moles) for 20 hr. After cooling, the mixture was poured into 200 ml. of 12 *N* HCl, and the acid solution was extracted several times with ether. The aqueous solution was then made alkaline and extracted again with ether. The ether solution was stripped of solvent and the residue (*ca.* 15 g., sirupy in appearance) was dissolved in 150 ml. of diethylene glycol containing 0.19 mole of potassium hydroxide. The solution (in a round-bottom flask equipped with a right angle tube to allow removal of vapors and gases) was heated to and maintained at 195–200° for 4 hr. The solution, following cooling, was poured into ice-water and extracted twice with ether. The ether solution, after solvent removal, was fractionally distilled, the cut having $n^{28}\mathrm{D}$ 1.4962 being found by gas chromatographic analysis to contain almost 99% *o*-neopentylanisole. The other fractions contained appreciable quantities of *o*-neopentylphenol.[24]

***o*-Neopentylphenol.**—*o*-Neopentylanisole (0.034 mole), mixed with 15 ml. of 48% hydrobromic acid in 40 ml. of glacial acetic acid, was heated at 170° for 5 hr. in a sealed Carius tube. The cooled contents were dissolved in aqueous sodium hydroxide and then adjusted by acid addition to pH 8. Extraction with ether followed by drying and distillation gave 3.7 g. of viscous liquid

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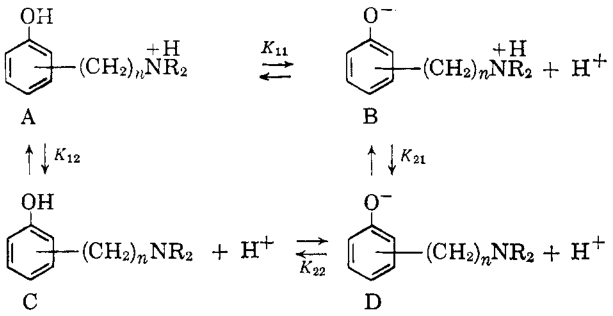
boiling at 130° (5 mm.), $n^{26}\text{D}$ 1.5148. When cooled, this liquid solidified and melted at 39°.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.43; H, 9.82; O, 9.74. Found: C, 80.0; H, 9.80; O, 9.70.

(b) **pK_a Determinations.**—The pK_a's of phenols containing one dissociable proton (or two in which the first and second ionization constants differ by several orders of magnitude; *e.g.*, catechol) were determined by potentiometric titration in 0.1 *M* KCl; the pK_{11}'s of the phenolamines (see Fig. 1) were determined spectrophotometrically.[25]



$$[C_0] = [A] + [B] + [C] + [D]$$

$$K_{11} = \frac{[B][H^+]}{[C_0] - [B] - [C]};\ K_{12} = \frac{[C][H^+]}{[C_0] - [B] - [C]}$$

$$K_A = K_{11} + K_{12}$$

Fig. 1.—Scheme for dissociation of aminophenols.

(c) **Determination of Reaction Velocities. (1) General Procedure.**—Approximately 0.0025 mole of phenolic compound, accurately weighed, was dissolved in approximately 10 ml. of 0.1 *M* KCl (or water if the phenol contained a charged group) in a 25-ml. volumetric flask. The solution was adjusted to pH 7 to 8 with a few drops of 1 *N* NaOH solution.

Exactly 3 ml. of the solution was stirred by a magnetic stirrer until the temperature had reached 25°. Ten microliters of 1% solution of GB in benzene (100 μg. of GB) were then pipetted into the reaction vessel. A stopwatch was started when half of the GB solution had entered the reaction vessel. The pH of the solution was maintained constant by the addition of 0.1 *N* NaOH (such that the over-all volume in the reaction mixture remained, for all practical purposes, the same). At various time intervals 0.1-ml. aliquots of the solution in the reaction vessel were pipetted into 10 ml. of 0.001 *M* acetic acid. The amount of unhydrolyzed GB in the acetic acid solution was determined by either of two enzymatic methods, both taking advantage of the anticholinesterase properties of GB.[26] In the first method an aliquot of the acetic acid solution (0.05 to 0.1 ml.) was added to a solution containing eel cholinesterase, allowed to react for 1 min., and the ability of the resulting solution to hydrolyze acetylcholine was determined, by previously published techniques.[27]

The second method employs eel cholinesterase with phenylacetate as the substrate.[28] An aliquot of the acetic acid solution of GB (0.1 ml.) is mixed with 3 ml. of 0.00488 *M* phenyl acetate in 0.1 *M* buffer, pH 7.00, followed by 0.1 ml. of eel cholinesterase. A control is run with the same reagents except that 0.1 ml. of solvent replaces the enzyme. After incubating for 20 min. at 25°, the increase in absorbance at 270 mμ relative to the control is determined. It can be shown that the absorbance is inversely proportional to the inhibitor (GB) concentration.[29] A plot of the reciprocal absorbance *vs.* time, from which the first-order rate constant, k_{obsd}, is determined, was linear over at least 75% decomposition of GB.

(2) **Calculations.**—In all cases, the phenols were present in sufficient excess so that their concentrations remained, to all intents and purposes, constant during the time of observation causing first-order kinetics. It was also established by rate determinations at different pH levels that the phenolate anion was the reactive species.

The bimolecular rate constants were calculated for phenols containing one dissociable proton from the equation

$$k_2 = \frac{k_{\text{obsd}}([H^+] + K_a)}{K_a[C_0]}$$

where k_2 is the bimolecular rate constant in l. mole^{-1} min.$^{-1}$, k_{obsd} is the first-order rate constant in min.$^{-1}$, K_a is the ionization constant of the phenol, and $[C_0]$ is the initial phenol concentration. The bimolecular rate constants of GB with the phenols having two simultaneously dissociating protons (the alkylaminophenols) were calculated from the equation

$$k_2 = k_{\text{obsd}}\,\frac{(K_A + [H^+])}{K_{11}[C_0]}$$

where k_2, k_{obsd}, $[C_0]$ are as previously indicated, and K_A and K_{11} are as described in Fig. 1.[30]

All rate constants are the average of at least two determinations run at different pH levels maintained constant by addition of base. The pH levels were such that only negligible concentrations of form D (Fig. 1) would be present. Their contributions to the rates were, therefore, neglected.

(3) **Determinations of the Bimolecular Rate Constant of *o*-*t*-Butylphenol (TBP) and GB.**—Owing to the extreme slowness of the reaction and the inability to attain sufficiently high concentrations of *o*-*t*-butylphenol in aqueous solution, the bimolecular rate constant for the reaction between it and GB was determined as follows.

A solution saturated with respect to TBP and containing GB was allowed to stand at constant pH for a time such that at least 99.9% of the GB had reacted. The solution was then analyzed for the TBP phosphonate (TBPP) content. It was assumed that the reactions between GB and hydroxyl ion and GB and the TBP ion proceeded simultaneously, so that

$$d[>\overset{\text{O}}{\overset{\|}{\text{P}}}\text{—OH}]/dt = k_1[\text{GB}][\text{OH}^-]$$

and

$$\frac{d[\text{TBPP}]}{dt} = k_2[\text{GB}][C_0] \times \frac{K_a}{K_a + [H^+]}$$

where $[C_0]$ is the concentration of TBP, K_a is the ionization constant of TBP, k_1 is the bimolecular rate constant of GB with hydroxyl ion in l. mole^{-1} min.$^{-1}$, and k_2 is the bimolecular rate constant of the reaction between TBP ion and GB in l. mole^{-1} min.$^{-1}$. At $t = \infty$

$$\frac{[>\overset{\text{O}}{\overset{\|}{\text{P}}}\text{—OH}]}{[\text{TBPP}]} = \frac{k_1[\text{OH}^-]}{k_2[C_0]} \times \frac{K_a + [H^+]}{K_a}$$

k_1, $[\text{OH}^-]$, $[C_0]$, K_a are known; [TBPP] is determined; $[>\overset{\text{O}}{\overset{\|}{\text{P}}}\text{—OH}]$ is equal to $[\text{GB}_0] - [\text{TBPP}]$.

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(25) J. T. Edsall and J. Wymann, "Biophysical Chemistry," Vol. I, Academic Press, Inc., New York, N. Y., 1958, p. 488 ff.

(26) The phosphonylated phenols which form by reaction with GB are potential anticholinesterases and might interfere with the determination of GB. However, it was found that only in the case of 4-dimethylsulfonium phenol was the rate of reaction of the phosphonylated products with cholinesterase comparable to that of GB. In this case, analysis for GB was carried out by extracting aliquots of the reaction mixture with 20 volumes of benzene and then determining the GB in the benzene extract by either of the two enzymatic methods described.

(27) H. S. Aaron, H. O. Michel, B. Witten, and J. I. Miller, *J. Am. Chem. Soc.*, **80**, 456 (1958).

(28) A. R. Main and W. C. Dauterman, *Nature*, **198**, 551 (1963), describe a spectrophotometric method employing phenyl acetate in which enzyme, substrate, and irreversible inactivator are allowed to react together as is done in the method described. Their method requires the rather difficult determination of changing slopes in contrast to the very simple time-independent relationship employed here.

(29) This statement is true provided that the substrate concentration remains constant. In practice, it was found that a graph of absorbance *vs.* the reciprocal of GB concentration was linear up to 0.7 absorbance unit at 270 mμ. Needless to say, only data within the limits of 0 and 0.7 absorbance unit were used as a measure of GB concentration.

(30) The assumption was made that species C (Fig. 1) does not materially contribute to the reaction rate, since (a) the fraction of species C is small as compared to B, especially in the *o*- and *p*-substituted phenols, and (b) a comparison of the relative reactivities of phenol and benzylamine indicated that, although the two are approximately of the same basic strength (pK_a's in 0.1 μ are 9.75, 9.49, respectively), the rate of GB with phenol is at least six times that of the rate of GB with benzylamine.

TABLE I

IONIZATION CONSTANTS AND RATE CONSTANTS OF GB REACTION WITH SUBSTITUTED PHENOLS

No.	Class	Compound, R =	pK_a (0.1 μ)[a]	k_2, l. mole^{-1} min.$^{-1}$
1	I	H	9.78	34.3
2	III	o-OH	9.30 (9.60)[b]	368.5
3	I	m-OH	9.32 (9.62)[b]	34.4
4	I	p-OH	9.82 (10.12)[b]	77.0
5	III	o-OCH_3	9.85	11.3
6	I	m-OCH_3	9.50	26.4
7	II	p-OCH_3	10.05	108.5
8	III	o-CH_3	10.10	10.8
9	I	m-CH_3	9.82	45.0
10	I	p-CH_3	10.10	54.6
11	III	o-NO_2	7.08	0.41
12	III	m-NO_2	8.23	15.3
13	I	p-NO_2	7.01	0.92
14	. . .	o-COO^-	. . .	[f]
15	I	m-COO^-	9.73[d]	44.7
16	I	p-COO^-	9.12[d]	16.0
17	II	o-NH_2	9.75	48.9
18	II	m-NH_2	9.86	30.7
19	I	p-NH_2	10.46	109.0
20	II	o-$\overset{+}{N}(CH_3)_3$	7.43	2.22
21	III	m-$\overset{+}{N}(CH_3)_3$	8.12	13.1
22	III	p-$\overset{+}{N}(CH_3)_3$	8.30	13.1
23	III	o-$CH_2\overset{+}{N}H_3$	8.89[c,d]	59.2
24	III	m-$CH_2\overset{+}{N}H_3$	9.06[c,d]	30.2
25	II	p-$CH_2\overset{+}{N}H_3$	9.14[c,d]	24.8
26	III	o-$CH_2\overset{+}{N}H(CH_3)_2$	8.62[c,d]	53.6
27	II	m-$CH_2\overset{+}{N}H(CH_3)_2$	8.88[c,d]	22.5
28	II	p-$CH_2\overset{+}{N}H(CH_3)_2$	8.83[c,d]	17.6
29	I	o-$CH_2\overset{+}{N}(CH_3)_3$	8.74	10.6
30	III	m-$CH_2\overset{+}{N}(CH_3)_3$	8.89	26.0
31	II	p-$CH_2\overset{+}{N}(CH_3)_3$	8.75	15.2
32	I	o-$CH_2CH_2\overset{+}{N}H_3$	9.19[c,d]	16.4
33	II	m-$CH_2CH_2\overset{+}{N}H_3$	9.27[c,d]	28.6
34	II	p-$CH_2CH_2\overset{+}{N}H_3$	9.39[c,d]	35.9
35	II	o-$CH_2CH_2\overset{+}{N}H(CH_3)_2$	8.75[c,d]	6.1
36	II	m-$CH_2CH_2\overset{+}{N}H(CH_3)_2$	9.24[c,d]	32.5
37	II	p-$CH_2CH_2\overset{+}{N}H(CH_3)_2$	9.46[c,d]	37.5
38	II	o-$CH_2CH_2\overset{+}{N}(CH_3)_3$	9.57	18.2
39	III	m-$CH_2CH_2\overset{+}{N}(CH_3)_3$	9.43	50.3
40	I	p-$CH_2CH_2\overset{+}{N}(CH_3)_3$	9.80	36.7
41	III	o-$CH_2CH_2CH_2\overset{+}{N}(CH_3)_3$	9.78	8.1
42	I	m-$CH_2CH_2CH_2\overset{+}{N}(CH_3)_3$	9.64	35.4
43	I	p-$CH_2CH_2CH_2\overset{+}{N}(CH_3)_3$	9.80	38.0
44	III	o-C_2H_5	10.20	11.2
45	III	o-$CH(CH_3)_2$	10.34	8.4
46	III	o-$CH_2C(CH_3)_3$	10.69	2.1
47	III	o-$C(CH_3)_3$	11.16	*ca.* 3
48	II	o-$CH_2CH_2CH_2\overset{+}{N}H_3$	9.51[c,d]	19.8
49	III	m-CHO	8.88	23.6
50	II	p-Br	9.17	26.7
51	II	p-$\overset{+}{S}(CH_3)_2$[e]	7.33	2.35
52	I	p-F	9.75	31.5
53	II	p-$CH_2CH(\overset{+}{N}H_3)C\text{–}O^-$	10.07[c,d]	75.0
54	II	p-$N(CH_3)_2$	10.10	92.4
55	III	3-Hydroxypyridine	5.37	0.21

[a] pK_a's determined by potentiometric titration in 0.1 M KCl at 25° (except as noted; see footnote *c*). [b] Figures in parentheses are pK_a values calculated to apply the statistical correction for polyfunctional groups (see ref. 31, p. 84). [c] Determined spectrophotometrically; see Experimental for procedure. [d] Ionization constant of the phenolic hydroxyl. [e] This compound was kindly supplied by C. C. Price, *J. Am. Chem. Soc.*, **80,** 3425 (1958). [f] Too slow to measure.

Results

Qualitative Analysis.—Table I lists the compounds investigated, their ionization constants in 0.1 M KCl at 25°, and their bimolecular rate constants with GB at 25°.

A Brønsted plot (pK_a *vs.* log k_2)[31] of the data in Table I is shown in Fig. 2. The compounds have been arbitrarily divided into three classes. Class I contains those compounds whose log k_2's differ by less than ±0.1 log unit from the values predicted from the equation log $k_2 = 0.589pK_a - 4.172$, the equation of the line shown.

Class II comprises those compounds whose log k_2's are more than ±0.1 but less than ±0.3 log unit from the values predicted from the equation and class III contains those compounds having log k_2 values greater than ±0.3 of the predicted values. The compounds in the various classes, the rates calculated from the equation log $k_2 = 0.589pK_a - 4.172$ using the pK_a of the appropriate phenol, the observed rates, and the differences in the logarithms of the observed and calculated k's are shown in Tables II, III, and IV. The k_c-values used in this report are the theoretical k_2 values calculated from this equation.

TABLE II

DATA ON COMPOUNDS IN CLASS I (LOG $k_2/k_c \leq \pm 0.1$ FROM PREDICTED)

Compound	Compound, R =	k_c, l. mole^{-1} min.$^{-1}$	k_2, l. mole^{-1} min.$^{-1}$	log k_2/k_c
6	m-OCH_3	26.5	26.4	−0.001
16	p-CO_2^-	15.95	16.0	.001
13	p-NO_2	0.91	0.92	.007
43	p-$CH_2CH_2CH_2\overset{+}{N}(CH_3)_3$	39.8	38.0	− .020
32	o-$CH_2CH_2\overset{+}{N}H_3$	17.4	16.4	− .026
40	p-$CH_2CH_2\overset{+}{N}(CH_3)_3$	39.8	36.7	− .035
10	p-CH_3	59.8	54.6	− .040
9	m-CH_3	40.9	45.0	.041
3	m-OH	31.2	34.4	.042
42	m-$CH_2CH_2CH_2\overset{+}{N}(CH_3)_3$	32.1	35.4	.043
19	p-NH_2	97.6	109.0	.048
29	o-$CH_2\overset{+}{N}(CH_3)_3$	9.46	10.6	.049
1	H	38.8	34.3	− .054
52	p-F	37.2	31.5	− .072
15	m-CO_2^-	36.2	44.7	.092
4	p-OH	61.5	77.0	.098

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(31) R. P. Bell, "Acid-Base Catalysis," Oxford at the Clarendon Press, Oxford, Eng., 1941, Chapter V, p. 82, ff.

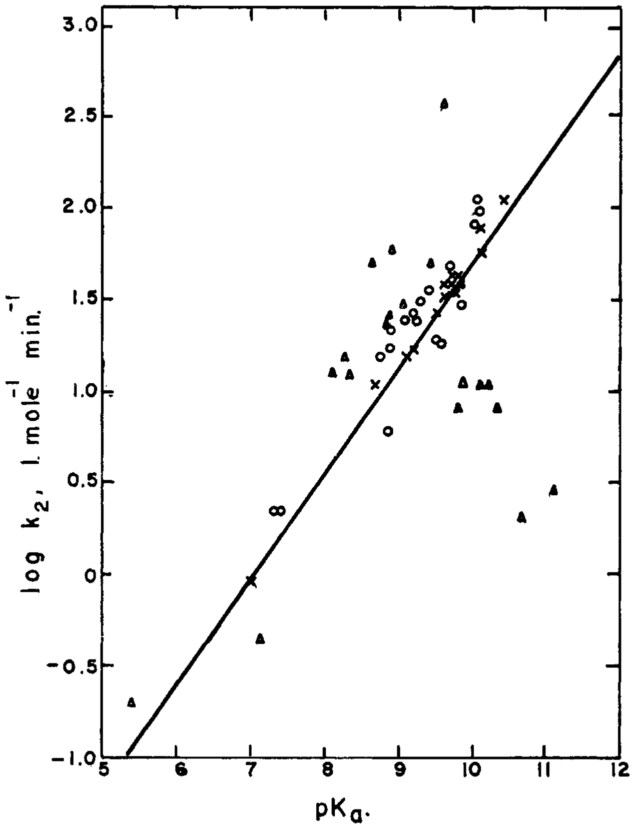


Fig. 2.—Brønsted plot of data in Table I: ×, class I; ○, class II; △, class III (see text).

The line shown in Fig. 2 is an arbitrary one, fitted to those compounds whose logarithmic rates, it is believed, are very nearly directly proportional to the basicities of the phenolate ions. The phenols chosen for construction of this line (compounds 1, 3, 4, 6, 9, 10, 13, 15, 16, 19, 52) have shown good linear relationships of reactivity (log k_2) with basicity in several series of reactions,[32] and the reactivity of GB with several classes of anions have been shown to follow the Brønsted catalysis law.[5c–e,7a]

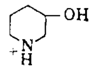
TABLE III

DATA ON COMPOUNDS IN CLASS II (LOG $k_2/k_c > \pm 0.1$ TO $< \pm 0.3$ FROM PREDICTED)

Compound	Compound, R =	k_c, l. mole^{-1} min.$^{-1}$	k_2, l. mole^{-1} min.$^{-1}$	log k_2/k_c
48	*o*-$CH_2CH_2CH_2\overset{+}{N}H_3$	26.9	19.8	−0.133
18	*m*-NH_2	43.3	30.7	− .150
35	*o*-$CH_2CH_2\overset{+}{N}H(CH_3)_2$	9.59	6.1	− .196
38	*o*-$CH_2CH_2\overset{+}{N}(CH_3)_3$	29.2	18.2	− .205
53	*p*-$CH_2\underset{COO^-}{\underset{\mid}{C}}H\text{–}\overset{+}{N}H_3$	57.4	75.0	.116
17	*o*-NH_2	37.2	48.9	.119
33	*m*-$CH_2CH_2\overset{+}{N}H_3$	21.5	28.6	.124
20	*o*-$\overset{+}{N}(CH_3)_3$	1.60	2.22	.142
37	*p*-$CH_2CH_2\overset{+}{N}H(CH_3)_2$	25.1	37.5	.173
25	*p*-$CH_2\overset{+}{N}H_3$	16.3	24.8	.182
54	*p*-$N(CH_3)_2$	59.8	92.4	.189
34	*p*-$CH_2CH_2\overset{+}{N}H_3$	22.9	35.9	.195
31	*p*-$CH_2\overset{+}{N}(CH_3)_3$	9.60	15.2	.199
50	*p*-Br	16.9	26.7	.199
28	*p*-$CH_2\overset{+}{N}H(CH_3)_2$	10.7	17.6	.216
51	*p*-$\overset{+}{S}(CH_3)_2$	1.36	2.35	.228
36	*m*-$CH_2CH_2\overset{+}{N}H(CH_3)_2$	18.7	32.5	.240
7	*p*-OCH_3	56.1	108.5	.286
27	*m*-$CH_2\overset{+}{N}H(CH_3)_2$	11.4	22.5	.295

TABLE IV

DATA ON COMPOUNDS IN CLASS III (LOG $k_2/k_c > \pm 0.3$ FROM PREDICTED)

Compound	Compound, R =	k_c, l. mole^{-1} min.$^{-1}$	k_2, l. mole^{-1} min.$^{-1}$	log k_2/k_c
11	*o*-NO_2	0.995	0.41	−0.385
5	*o*-OCH_3	42.6	11.3	− .578
41	*o*-$CH_2CH_2CH_2\overset{+}{N}(CH_3)_3$	38.8	8.1	− .680
8	*o*-CH_3	59.8	10.8	− .742
44	*o*-C_2H_5	68.5	11.2	− .786
45	*o*-$CH(CH_3)_2$	82.8	8.4	− .994
46	*o*-$CH_2C(CH_3)_3$	133	2.1	−1.802
47	*o*-$C(CH_3)_3$	252	*ca.* 3	*ca.* −1.9
49	*m*-CHO	11.4	23.6	0.316
24	*m*-$CH_2\overset{+}{N}H_3$	14.6	30.2	.316
39	*m*-$CH_2CH_2\overset{+}{N}(CH_3)_3$	24.1	50.3	.320
55		0.098	0.21	.331
30	*m*-$CH_2\overset{+}{N}(CH_3)_3$	11.6	26.0	.350
22	*p*-$\overset{+}{N}(CH_3)_3$	5.21	13.1	.400
21	*m*-$\overset{+}{N}(CH_3)_3$	4.73	13.1	.507
12	*m*-NO_2	4.73	15.3	.510
23	*o*-$CH_2\overset{+}{N}H_3$	11.6	59.2	.708
26	*o*-$CH_2\overset{+}{N}H(CH_3)_2$	8.04	53.6	.824
2	*o*-OH	30.3	368.5	1.085

Compounds possessing formal charges or *ortho* substituents were not used in construction of the "base" line inasmuch as the former might be expected, because of their interaction with the polar solvent, and the latter, by steric interactions, to behave abnormally.

Of the fifty-four compounds listed, sixteen fall into class I, nineteen into class II, and nineteen into class III. In class I, in addition to those compounds used for construction of the base line, are *o*-aminoethyl- and *o*-trimethylammoniomethylphenols, *m*- and *p*-trimethylammoniopropylphenol, and *p*-triethylammonioethylphenol. Class II can be divided into two subclasses: those whose rates are less than might be expected from their basicities (log k_2/k_c is negative—class IIa) and those whose rates give positive deviations from the "norm" (class IIb). The former subclass contains mostly *o*-substituted aminoalkylphenols; the latter, mostly *p*-substituted aminoalkylphenols, although *p*-OCH_3, *p*-Br, *p*-$N(CH_3)_2$ also appear with this group. Of the three *m*-substituted aminoalkylphenols appearing in class IIb, two (compounds 36 and 27) have reactivities close to those falling into class III.

Class III is also comprised of two subclasses. Class IIIa consists only of *o*-substituted phenols; the com-

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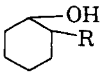
[32] D. R. Boyd and E. R. Marle, *J. Chem. Soc.*, **105**, 2117 (1914); L. J. Goldworthy, *ibid.*, 1254 (1926); H. L. Bassett, *ibid.*, 2516 (1931); 1313 (1930); H. L. Bassett and A. O'Leary, *ibid.*, 2945 (1932); G. H. Green and J. Kenyon, *ibid.*, 1589 (1950).

TABLE V

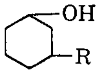
ortho-SUBSTITUTED ALKYLAMINO- AND AMMONIOPHENOLS



Compd.	Compd., R =	Log k_2/k_c	Compd.	Compd., R =	Log k_2/k_c	Compd.	Compd., R =	Log k_2/k_c
17	$-NH_2$	+0.119				20	$-\overset{+}{N}(CH_3)_3$	+0.142
23	$-CH_2\overset{+}{N}H_3$	+ .708	26	$-CH_2\overset{+}{N}H(CH_3)_2$	+0.824	29	$-CH_2\overset{+}{N}(CH_3)_3$	+ .049
32	$-CH_2CH_2\overset{+}{N}H_3$	− .026	35	$-CH_2CH_2\overset{+}{N}H(CH_3)_2$	−0.196	38	$-CH_2CH_2\overset{+}{N}(CH_3)_3$	− .205
48	$-CH_2CH_2CH_2\overset{+}{N}H_3$	− .133				41	$-CH_2CH_2CH_2\overset{+}{N}(CH_3)_3$	− .680

TABLE VI

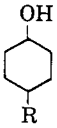
meta-SUBSTITUTED ALKYLAMINO- AND AMMONIOPHENOLS



Compd.	Compd., R =	Log k_2/k_c	Compd.	Compd., R =	Log k_2/k_c	Compd.	Compd., R =	Log k_2/k_c
18	$-NH_2$	−0.150	27	$-CH_2\overset{+}{N}H(CH_3)_2$	+0.295	30	$-CH_2\overset{+}{N}(CH_3)_3$	+ 3.50
24	$-CH_2\overset{+}{N}H_3$	+ .316	36	$-CH_2CH_2\overset{+}{N}H(CH_3)_2$	+0.240	39	$-CH_2CH_2\overset{+}{N}(CH_3)_3$	+ .320
33	$-CH_2CH_2\overset{+}{N}H_3$	+ .124	21	$-\overset{+}{N}(CH_3)_3$	+0.507	42	$-CH_2CH_2CH_2\overset{+}{N}(CH_3)_3$	+ .043

TABLE VII

para-SUBSTITUTED AMINOALKYL- AND AMMONIOPHENOLS



Compd.	Compd., R =	Log k_2/k_c	Compd.	Compd., R =	Log k_2/k_c	Compd.	Compd., R =	Log k_2/k_c
19	$-NH_2$	+0.048	54	$-N(CH_3)_2$	+0.189	22	$-\overset{+}{N}(CH_3)_3$	+0.400
25	$-CH_2\overset{+}{N}H_3$	+ .182	28	$-CH_2\overset{+}{N}H(CH_3)_2$	+ .216	31	$-CH_2\overset{+}{N}(CH_3)_3$	+ .199
34	$-CH_2CH_2\overset{+}{N}H_3$	+ .195	37	$-CH_2CH_2\overset{+}{N}H(CH_3)_2$	+ .173	40	$-CH_2CH_2\overset{+}{N}(CH_3)_3$	− .035
53	$-CH_2\underset{\substack{\vert \\ COO^-}}{C}H\overset{+}{N}H_3$	+ .116				43	$-CH_2CH_2CH_2\overset{+}{N}(CH_3)_3$	− .020

pounds in this class are less reactive than one would predict from their basicities. Class IIIb consists of three *o*-substituted phenols, six *m*-substituted phenols, and one *p*-substituted compound; these compounds show higher reactivities than expected. The largest deviations from the line shown in Fig. 2 are given by *o*-substituted phenols; the deviations are positive if the *ortho* substituents contain groups which are capable of hydrogen bonding (compounds 23, 26, and 2) and negative when the *ortho* substituent is alkyl and alkoxy, with the deviation becoming greater as the size of the alkyl group increases (*cf.* compounds 5, 8, 44, 46, 47).

The substituted amino-, aminoalkyl-, and ammoniophenols are arranged in order of increasing distance of separation of the phenolate oxygen and the nitrogen atom in Tables V (*o*), VI (*m*), and VII (*p*). The deviations of each compound (log k_2/k_c) from the "base" line are also given. It is noteworthy that, for the *o*-substituted compounds capable of hydrogen bonding (Table V), the amino*methyl*phenols (compounds 23 and 26) show large positive deviations, whereas the amino*ethyl*phenols (compounds 32 and 35) and amino*propyl*phenol (compound 48) are less reactive than would be predicted from their respective basic strengths. It can be argued then, that, if hydrogen bonding is a necessary prerequisite for enhanced reactivity, then the spatial arrangement for hydrogen bonding to the GB molecule is poor if there is more than one methylene group separating the aromatic carbon from the locus of positive charge. The ineffectiveness of a hydrogen capable of bonding if separated from the aromatic carbon by two methylene groups is also shown by the almost identical magnitudes of deviation shown by compounds 35 and 38, one of which, 38, is incapable of hydrogen bonding. Inasmuch as the deviations shown by compounds 35 and 38 are only slightly negative whereas *o*-substituted phenols of like bulk possessing no charge show much larger deviations (*cf.* Table IV, especially compounds 44–47 inclusive), a further inference from these data is that there must be at least two distinct and opposing forces affecting the reactivity of *o*-substituted aminoalkylphenols, one increasing the reactivity, the other decreasing it.

Associated with the former is the presence of a cationic site in the molecule, the increase becoming larger as the distance between the positive charge and the site of high electron density (phenolate oxygen) decreases. Associated with the latter is the bulk of the *ortho* substituent.

The data in Tables VI and VII show a smooth decrease in the log k_2/k_c values as the distance between the positive charge and phenolate oxygen increases. This relationship is further demonstrated by comparing the deviations of the same substituents in the *meta* and the *para* positions (*e.g.*, compounds 21 and 22; 30 and 31; 39 and 40; etc.). In contrast to the deviations shown by *ortho*-substituted phenols, the deviations of *meta*- and *para*-substituted ones approach zero (the slightly negative deviations shown by compounds 40 and 43 (Table VII) are considered to be of no significance). In the *para* series, compound 40 approaches zero; in the *meta*, compound 42 approaches zero. The distance between the phenolate oxygen and the nitrogen can be considered approximately equal for the two compounds inasmuch as the *m*-substituted compound has one more methylene group between the nitrogen atom and the ring carbon. Thus, at this distance the contribution of the cationic group to the reactivity is, to all intents and purposes, negligible, the reactivity of the molecule being equal to that predicted from the basicity of the phenolate ion.

Noteworthy also is the fact that there is no great difference in the log k_2/k_c's among the *m*-substitued compounds 24, 27, and 30 (Table VI) and among the *p*-substituted ions 25, 28, 31 (Table VII), which suggests that the presence of a dissociable proton is not important to the reactivity in these classes of compounds. But a comparison of the reactivities of compounds 33, 36, and 39 would argue against such a conclusion. Nevertheless, the preponderance of the data suggests that any explanation of the enhancement of reactivity shown by the dipolar ions includes electrostatic phenomena.[33]

Mathematical Relationships.—As a first approximation, the rate enhancement shown by *m*- and *p*-substituted positively charged phenols is assumed to be related to the inverse square of the distances separating the charge centers in the dipolar ion, *i.e.*

$$[\log (k_2/k_c)]_e = c/d^2 \qquad (1)$$

where k_2 and k_c are as previously defined and $[\log k_2/k_c]_e$ is the deviation due to electrostatic effects, c is a constant, and d is the distance separating the charges.

By substitution of the log k_2/k_c values for *m*- and *p*-trimethylammoniophenols (in contrast to the phenols in which the positively charged function is at the end of a flexible chain of varying length, the charged function in *m*- and *p*-trimethylammoniophenol is fixed in space; a reasonable estimate, therefore, can be made of the distance of separation of the charges in these compounds using molecular models), along with their respective distances of separation of charges into eq. 1, one can calculate a value for the constant c; using the calculated c-value, $[\log k_2/k_c]_e$ for *o*-trimethylammoniophenol can then be calculated. Calculated values for c and $[\log k_2/k_c]_e$[34] for the *o*-trimethylammoniophenol are shown in Table VIII.

TABLE VIII

$[\text{LOG } k_2/k_c]_e$ VALUE FOR *o*-TRIMETHYLAMMONIOPHENOL CALCULATED FROM DATA ON *m*- AND *p*-TRIMETHYLAMMONIOPHENOL

	$\frac{1^a}{d^2}$	c^b	$[\log k_2/k_c]_e$
$o\text{-}\overset{+}{N}(CH_3)_3$	0.141	$(12.7)^c$	$(1.79)^d$
$m\text{-}\overset{+}{N}(CH_3)_3$	.0406	12.5	0.507
$p\text{-}\overset{+}{N}(CH_3)_3$	.0313	12.8	0.400

[a] d is measured from scale models constructed using bond distances and bond angles given by L. Pauling, "Nature of the Chemical Bond," 2nd Ed., Cornell Univ. Press, Ithaca, N. Y., 1940. [b] c is the constant in the equation log $k_2/k_c = c/d^2$. [c] Average value of 12.5 and 12.8. [d] Calculated from eq. 1.

Thus, according to our model, the rate of the reaction between trimethylammoniophenol and GB should be approximately 1.8 log units higher than that calculated from the equation of the line in Fig. 2. The marked decrease in reactivity, however, shown by the different *o*-alkylphenols suggests that the difference in the logarithms of the rates of the charged phenols be treated as the algebraic sum[35] of the two effects, steric and electrostatic, *i.e.*

$$\log k_2/k_c = [\log k_2/k_c]_s + [\log k_2/k_c]_e \qquad (2)$$

where log k_2/k_c is as previously defined; $[\log k_2/k_c]_s$ is the deviation due to steric effect and generally negative, whereas $[\log k_2/k_c]_e$, the deviation attributable to the presence of a cationic site, is positive.

If it can be assumed that the steric effect due to the trimethylammonio group is the same as of its isostere, the *t*-butyl group, then the value of the log k_2/k_c for *o*-trimethylammoniophenol should be approximately $-1.9 + 1.8 = -0.1$. The value, thus calculated, is sufficiently close to that actually found (0.14) to give the treatment shown herein some validity.

Assuming that the deviations from the "base" line of other *o*-aminoalkylphenols can be described by eq. 2, then the $[\log k_2/k_c]_e$ can be estimated from the experimentally determined log k_2/k_c values (Table II–IV) with the $[\log k_2/k_c]_s$ values assumed to be equal to the log k_2/k_c values of phenols containing isosteric groups without cationic sites. Table IX shows the results of such calculations.

The electrostatic contribution in this series of compounds is not too different from that calculated for *o*-trimethylammoniophenol.[36]

The relative constancy[37] of the $[\log k_2/k_c]_e$ values

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(33) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 81. The use of the word 'electrostatic" will refer in this paper exclusively to ion–ion interaction.

(34) $[\text{Log } k_2/k_c]_e$ is not to be confused with $[\log k_2/k_c]$ shown in Table II! The former value represents the deviation from the base line that would be expected if the only factor of importance (other than basicity) in the reactivity of *o*-trimethylammoniophenolate ion with GB were related to electrostatic effects.

(35) *Cf.* R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," edited by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13; G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1941, p. 193.

(36) One could infer from this that the distance of charge separation in the compounds 20, 26, and 29 is of similar magnitude. It is interesitng that the calculated distance of separation of charge from eq. 1 to give a log k_2/k_c of 1.85 units is 2.6 Å.; the measured distance (scale model) in *o*-dimethylaminoethylphenol, assuming a planar configuration and positioning of the nitrogen such that it is closest to the oxygen, is 2.5 Å.

(37) The fact that *o*-aminomethylphenol has a somewhat lower $[\log k_2/k_c]_e$ value is not disturbing; it is felt that the charged groups are actually closer in the compounds 26 and 29 than in compound 23 due to exclusion of solvent molecules by the former [*cf.* A. G. Evans and S. D. Hamann, *Trans. Faraday Soc.*, **47**, 34 (1951)]. The slightly larger distance of charge separation in compound 23 would account for the lower $[\log k_2/k_c]_e$ value calculated for this compound.

TABLE IX

ELECTROSTATIC CONTRIBUTIONS TO REACTION RATES OF AMINOMETHYLPHENOLS CALCULATED FROM EQUATION 2

No.	Substituent	log k_2/k_0, found	Steric, found	Electrostatic, calcd.
23	$o\text{-}CH_2\overset{+}{N}H_3$	0.71	-0.79^a	$+1.50$
26	$o\text{-}CH_2\overset{+}{N}H(CH_3)_2$	.82	-1.04^b	$+1.86$
29	$o\text{-}CH_2\overset{+}{N}(CH_3)_3$	.05	-1.80^c	$+1.85$

[a] Assumed to be equal to $o\text{-}C_2H_5$ (compound 44, Table IV). [b] Assumed to be equal to $CH_2CH(CH_3)_2$; the steric value for this group was estimated from relationships developed by Taft, ref. 35, p. 601, and the data given in Table I. [c] Assumed to be equal to $o\text{-}CH_2C(CH_3)_3$ (compound 46, Table IV).

suggests that hydrogen bonding by the aminoalkylphenol to the GB is not important to the reactivity; the enhanced reactivity can be adequately explained solely on electrostatic grounds.

The additivity hypothesis satisfactorily accounts for, at least qualitatively, the results found for other *o*-substituted aminoalkylphenols, compounds 48, 35, and 38 (Table III), and compound 41 (Table IV). As the distance between the charges increases, the electrostatic contribution resulting in enhanced rate may be expected to become less, whereas the bulk effect (retarding) will be greater. The net effect is to give negative deviations from the base line, but less than those which might be expected due to a bulk steric effect.

Linear Free Energy Relationships.—Table X lists the slope (ρ) of the regression line in the conventional Hammett plot (log k/k_0 *vs.* σ)[38,39] of fourteen *m*- and *p*-substituted phenols, the standard deviation (s) from the line, the correlation coefficient (r), and the intercept of the regression line with the ordinate at $\sigma = 0$ (log k_0).

TABLE X

SLOPE, STANDARD DEVIATION, CORRELATION COEFFICIENT, AND INTERCEPT OF REGRESSION LINE[a] OBTAINED FROM THE PLOT LOG k/k_0 *vs.* σ AT $T = 25°$, $\mu = 0.1$

$\rho = -1.0902$ $s = 0.150$
$r = 0.961$ $\log k_0 = 1.4912$
$n = 14$

[a] For method of calculation, see ref. 39; k is the bimolecular reaction rate constant of the substituted[b] phenol with GB; k_0 is the rate of the unsubstituted phenol reaction. [b] Substituents: H, $p\text{-}NH_2$, $p\text{-}N(CH_3)_2$, $p\text{-}OH$, $p\text{-}OCH_3$, $p\text{-}F$, $p\text{-}Br$, $p\text{-}NO_2$, $p\text{-}CO_2^-$ $p\text{-}CH_3$, $m\text{-}NH_2$, $m\text{-}OH$, $m\text{-}OCH_3$, $m\text{-}CH_3$.

Inclusion of phenols containing the substituents *m*- and $p\text{-}(CH_3)_3\overset{+}{N}$, $p\text{-}\overset{+}{S}(CH_3)_2$, *m*-CHO, $m\text{-}CO_2^-$, and $m\text{-}NO_2$,[40] with the aforementioned fourteen phenols gives a line of smaller slope ($\rho = -0.8814$), with a lower correlation coefficient ($r = 0.924$), a higher standard deviation ($s = 0.183$), and a log k_0 value of 1.566. The correlation of the reaction rate data of *o*-alkyl-substituted phenols with Taft's[41] steric substituent constants (E_s, Table XI) is excellent.

TABLE XI

SLOPE, STANDARD DEVIATION, CORRELATION COEFFICIENT, AND INTERCEPT OF THE REGRESSION LINE[a] OBTAINED FROM THE PLOT OF LOG k/k_0 *vs.* E_s AT $T = 25°$, $\mu = 0.1$

$\rho = -0.3938$ $s = 0.03873$
$r = 0.9968$ $\log k_0\,(o\text{-}CH_3) = -0.4740$
$n = 6$

[a] For methods of calculation see ref. 39; k is the bimolecular rate constant of the substituted phenol[b] with GB; k_0 is the rate constant of the unsubstituted phenol. [b] Substituents: H, $o\text{-}CH_3$, $o\text{-}C_2H_5$, $o\text{-}CH(CH_3)_2$, $o\text{-}C(CH_3)_3$, $o\text{-}CH_2C(CH_3)_3$.

Discussion

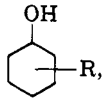
For purpose of further discussion, it is well to summarize the qualitative results of our study. (a) The nucleophilic displacement capability of a phenolate increases with the basicity of the anion (slope $\simeq$ 0.6). (b) Cationic sites in the phenol increase the reactivity of the phenolate ion and the increase is related to the distance between cationic and anionic sites. (c) There are marked steric (bulk) effects due to *ortho* substituents which lower the reactivity of the phenol. (d) Substances in the *ortho* position which are capable of hydrogen bonding can markedly increase the rate constant. (e) The reactivity of phenols in which the *ortho* substituent contains a cationic site can be adequately explained on the basis that two effects, opposite in their manifestations on the reactivity, are operative, *viz.*, b and c.

The enhanced reactivity shown by the *p*-methoxy, *p*-dimethylamino-, and *p*-bromophenols may be attributed to the polarizabilities of the substituents[42] which aid in bond formation in the transition state.

The abnormal reactivities shown by the *m*-nitro- and -aldehydophenols are thought to be due to favorable entropy effects caused by a release of "frozen" water in the formation of the transition state. In the case of *m*-nitrophenol, our conclusion is based upon the following.

First, the role of water in the reactivity of *m*-nitrophenol may be seen from the data in Table XII, in which a comparison is made of the reactivity of GB with selected phenols in *aqueous solution* with the re-

TABLE XII

RELATIVE RATES OF REACTION BETWEEN SUBSTITUTED PHENOLS,  AND GB AND ACETYL BROMIDE (REACTION RATE WITH PHENOL = 1)

R	pK_a	Relative reaction rate GB	 $CH_3\overset{O}{\overset{\|}{C}}Br$
o-Nitro	7.08	0.013	Very slow
m-Nitro	8.23	.53	0.085^a
p-Nitro	7.01	.029	$.031^a$
$o\text{-}OCH_3$	9.85	.35	$.37^a$
$m\text{-}OCH_3$	9.50	.83	$.97^a$
$p\text{-}OCH_3$	10.05	3.39	4.83^a
$o\text{-}CH_3$	10.10	0.33	0.57^b
$m\text{-}CH_3$	9.82	1.37	1.71^b
$p\text{-}CH_3$	10.10	1.71	2.35^b

[a] Data of H. L. Bassett and A. O'Leary, *J. Chem. Soc.*, 2945 (1932). [b] Data of H. L. Bassett, *ibid.*, 2516 (1931).

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(38) Reference 33, p. 186 ff.

(39) The σ-values are those of H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(40) The σ-values for these substituents are again those of Jaffé, ref. 39, except for the $p\text{-}(CH_3)_2\overset{+}{S}$ ($\sigma = 1.16$) which is that of F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 87 (1956). These groups are reported separately because of the uncertainty of their σ-values, especially as phenolic substituents and for reactions in aqueous solution.

(41) R. A. Taft, ref. 35, p. 598.

(42) A. E. Remick, "Electronic Interpretations of Organic Chemistry," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1949 Chapter V.

activity of acetyl bromide with the same phenols in *ethyl acetate*.

These data show a very great similarity in the displacement reaction of acetyl bromide and GB by phenolate ions; the similar dependence of the rate with both substrates upon basicity of the phenolate ion, the polarizabilities of the substituents, and bulk steric effects is clearly indicated. Small differences in the magnitude of effects can be attributed to the higher polarizability of the bromine as compared to the fluorine. Only the difference in the relative rates of reaction between *m*-nitrophenol and GB and acetyl bromide is outstanding, the former being much too high for its basicity, while the latter is approximately what might be expected from its basicity.

Now, the decreased acidity of *m*-nitrophenol in aqueous solution relative to *o*- and *p*-nitrophenol has been shown to be due to difference in the entropy of ionization of the compounds.[43] The anion of *m*-nitrophenol (relative to the undissociated *m*-nitrophenol) was pictured as being more effective in orienting the neighboring water molecules than were the anions of *o*- and *p*-nitrophenol (relative to their undissociated phenols). Thus, one may infer, at least in comparing *m*-nitrophenol and *p*-nitrophenol, that there is a greater loss of solvated water upon neutralization of the charge on the phenolate oxygen (whether by a proton or a Lewis acid, GB) by the *meta*- than by the corresponding *para*-substituted compound. Since *p*-nitrophenol falls in the "base" line, the deviation shown by the *m*-nitrophenol may be attributed to a favorable entropy factor.

The possibility of an entropy effect of this nature being responsible for the enhanced reactivity of the catechols is worthy of investigation since although one is still faced with hydrogen bonding as the only plausible explanation for the abnormal reactivity for this series of compounds, nevertheless, the argument for hydrogen bonding has not been strengthened by these studies.

Of particular significance and interest is the answer to the question, "Why do charged phenols show increased activity?"

In a relationship of log k_2 *vs.* pK_a such as is used in this report, it is assumed that one can obtain a measure of the basic strength of a nucleophile to a substrate from the pK_a of its conjugate acid in aqueous solution. While the assumption is valid for many nucleophiles (see ref. 5 and 7), it is our belief that the pK_a of a positively charged phenol is not a correct measure of the basicity of the corresponding phenolate ion to a neutral substrate; that, in fact, the basicity of the charged phenolate ion is somewhat larger than is indicated by the pK_a of the conjugate acid. This can be seen by an analysis of the ionization process. In the case of a positively charged phenol, the dissociation of the proton is facilitated (relative to the dissociation of an uncharged phenol) by at least these factors: (a) the electron-withdrawal (inductive) effect of the charged group; (b) a repulsion of the proton by the positively charged cationic group, assisting in breaking the OH bond; and (c) a repulsion of the proton preventing the back formation of the undissociated phenol. While the magnitude of each of these effects is difficult to assess, it is certain that the extent of ionization depends upon their individual contributions and that the ionization of a positively charged phenol would be less than observed if repulsion forces were absent. Similarly, the basicity of the phenolate oxygen in a positively charged phenolate ion would be greater than is indicated by the pK_a of the conjugate acid if there were no repulsive forces between the substrate and the phenolate ion. The basicity of the phenolate oxygen appears to be less only because the hydronium ion it seeks to attract is repelled by the cationic moiety in the nucleophile. Thus, the effective basicity of the charged phenolate ion would be greater (since there are no repulsive forces) to a neutral substrate than to the positively charged hydronium ion.

It is, of course, attractive to speculate that this is the reason for the high reactivity shown by enzymes to neutral substrates. Further evidence on the charge effect has been obtained with alkylamino- and di(alkylamino)catechols.[44] The enhanced reactivity of the latter compounds (which contain two cationic groups) can be explained on the assumption that each cationic site contributes to excess reactivity in accordance with the distance of separation of charges as shown previously.

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(43) L. P. Fernandez and L. G. Hepler, *J. Am. Chem. Soc.*, **81**, 1783 (1959).

(44) To be published.